

REMARKS

Claims 27, 29-50 and 52 are pending in the present application. Claims 1-26, 28, and 51 have been canceled. Reconsideration of the application is respectfully requested in view of the following responsive remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

In the office action of December 4, 2007, the following actions were taken:

(1) Claims 27, 29, 31-50, and 52 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Cserhati and Hollo, *Intl. J. Pharmaceutics* (1994) 08:69-75 (hereinafter "Cserhati") in view of Links and Lewis, *Drugs* (1999) 57(3):293-308 (hereinafter "Links"); and

(2) Claims 27 and 30 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Cserhati in view of Links and Baumann and Preiss, *J. Chromatography* (2001) 764:173-192 (hereinafter "Baumann").

It is respectfully submitted that the presently pending claims be examined and allowed. Applicants submit that each and every amendment herein, and throughout the prosecution of the present application is fully supported by the specification as originally filed, and that no new matter has been added.

Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 27, 29-50, and 52 under 35 U.S.C. 103(a) as being unpatentable over several references.

The Applicant does not deem it necessary to recite the entire case law standard required in order to establish a *prima facie* case of obviousness. However, the Applicant would like to briefly remind the Examiner of the required three criteria for a *prima facie* case of obviousness, namely 1) that the asserted references as modified or combined must teach or suggest each and every element of the claimed invention, 2) that the asserted references as modified or combined must provide a sufficient likelihood of successfully making the modification or combination, and 3) that the Examiner must identify a reason for the modification or combination asserted. The recent *KSR* Supreme Court case does not change this basic analysis.

With the above background in mind, Applicants submit that the cited references do not support a *prima facie* case for obviousness.

Cserhati in view of Links

Claims 27, 29, 31-50, and 52 were rejected under 35 U.S.C. § 103 as being unpatentable over Cserhati in view of Links.

The Cserhati and Links references, when combined, do not teach or suggest all of the elements of independent claim 27. The Applicant wishes to acknowledge the Examiner's point in identifying oxazaphosphorine in the cited art by specific reference for the Applicant to consider. Cserhati discusses the interactions of taxol and other anticancer drugs, including cyclophosphamide, with hydroxypropyl- β -cyclodextrin (HP β CD) in forming complexes. The disclosure further reports that the capacity of drugs to form inclusion complexes with HPBCD differs considerably according to chemical structure. The findings of Cserhati include that "the solubility of taxol can be enhanced by HP β CD" as "the complex [is] more hydrophilic than the uncomplexed drug." See page 72 and Abstract, respectively. Cserhati reports that the intensity of interaction is reported to increase with increasing hydrophobicity of the drug. See Abstract. As such, one skilled in the art would conclude that HP β CD is more useful in increasing the hydrophilicity of hydrophobic drugs. However, oxazaphosphorines, in accordance with the present invention, are hydrophilic and even hygroscopic. For example, ifosfamide has a solubility in water of 100 mg/ml. As such, the teachings of Cserhati can be said to teach away from the present invention.

As the Applicant has raised the issue of teaching away, the Applicant would like to review the current case law regarding teaching away for the Examiner's convenience. The Court of Appeals for the Federal Circuit has clearly stated that "an applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." In re Petersen, 315 F.3d 1325, 1331 (Fed. Cir. 2003). The Court has also stated that "[w]e have noted elsewhere, as a 'useful general rule,' that references that teach away cannot serve to create a *prima facie* case of obviousness." (emphasis added) McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1354 (Fed. Cir. 2001). In identifying the appropriate standard for teaching away, the Court has further stated:

“A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be **discouraged from following the path set out in the reference**, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, **a reference will teach away if it suggests that the line of development** flowing from the reference's disclosure **is unlikely to be productive** of the result sought by the applicant.” (emphasis added) In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

In the present case, a person of ordinary skill in the art would be discouraged from using HP β CD to increase the hydrophilicity of the present oxazaphosphorines since they are already hydrophilic. Additionally, a person of ordinary skill in the art would be discouraged from using HP β CD to stabilize a hydrophilic oxazaphosphorines since Cserhati teaches that hydrophobic forces are responsible for complex formation. See Abstract. Therefore, complexing these oxazaphosphorines with HP β CD would not be obvious to one skilled in the art based on Cserhati.

Additionally, the method disclosed in Cserhati is quite different that the present claimed method. Specifically, Cserhati teaches that the Cyclophosphamide and HP β CD comes in contact in aqueous methanol medium in preparing a solution for loading and for development of chromatogram, and on a TLC plate (i.e. in presence of active silica) impregnated in n-hexane – paraffin 95:5 v/v. See page 70, 1st col. “Experimental” section. However, the presently claimed invention is a composition prepared for intravenous use comprising aqueous solution of oxazaphosphorine antineoplastic, HP β CD, and mesna.

Furthermore, while mesna is taught in Links as a chemoprotectant, it is clear from this disclosure that mesna is administered separately from the drugs even though such administration can be begin prior to or concurrent with the administration of cyclophosphamide. See page 304, 1st col., 2nd ¶; 2nd col., 3rd ¶; page 305, 1st col., 1st ¶. To be clear, Links’ discussion over pages 304 and 305 describe separate administrations of the drug and mesna. The two drugs are stored separately and administered separately, in accordance with the current state of the art. However, more importantly, Links also discloses that mesna must be administered beyond the administration of ifosfamide or cyclophosphamide. See page 304, 2nd col., 3rd ¶.

As such, the disclosure in Links not only fails to disclose the present compositions but actually teaches away from such compositions. Specifically, Links states that “it is necessary to continue treatment with mesna beyond the completion of administration of ifosfamide or

cyclophosphamide.” See page 304, 2nd col., 3rd ¶. Additionally, Link explicitly states that the half life of mesna is 1 hour, further teaching away from a single administration of mesna and ifosfamide. See page 304, 2nd col., “Administration of Schedules.” Such disclosure teaches away from a combined ifosfamide/mesna composition since Links requires continuing administration of mesna after completion of the ifosfamide administration. As previously discussed, a reference that teaches away from the present invention cannot be used to establish a *prima facie* case of obviousness. Specifically, one of ordinary skill in the art would be discouraged from combining ifosfamide with mesna in a single composition since Links teaches a continuing administration of mesna after completion of the ifosfamide administration.

Furthermore, the Applicant submits that there is no suggestion in either reference of combining mesna in a stable solution with oxazaphosphorines and HP β CD. The difficulties involved in making a ready-to-administer formulation containing cyclophosphamide or ifosfamide along with mesna are known in the art and discussed in the Applicants’ specification. Given the relative doses of mesna and cyclophosphamide or ifosfamide required for efficacy, the long-felt need of such formulations are clear, particularly when continuous administration of neoplastic drug is indicated.

Additionally, the Applicant would like to address the Examiner’s optimization arguments. The Applicant submits that optimization starts after the “process that works” is known. The present process was not known, nor could one of ordinary skill in the art have been able to perform the present process based on the disclosures of the prior art. As such, the Applicant submits that it is not possible to optimize the present process without first having the process. The present invention is altogether a different process than that described in the art, as previously discussed. As such, the Applicant submits that mere optimization of the art could not lead one skilled in the art to arrive at the present invention.

In view of the above, Applicants assert that the cited references do not support a *prima facie* case for obviousness of claim 27 or any of the claims depending from it.

Cserhati in view of Links and Baumann

Claims 27 and 30 were also rejected under 35 U.S.C. § 103 as being unpatentable over Cserhati in view of Links and Baumann. Baumann is cited as teaching ifosfamide and

cyclophosphamide as commonly used oxazaphosphorines in chemotherapy. However, Baumann does not remedy the deficiency of Cserhati and Links to teach or suggest a stable, parenterally administrable formulation containing both cyclophosphamide or ifosfamide and mesna. The Applicant renews the above arguments with respect to the present combination. As such, the Applicant asserts that the cited references do not support a *prima facie* case for obviousness of pending claims 27 or 30.

The Applicant respectfully asserts the Examiner has not satisfied the requirement for establishing a case of *prima facie* obviousness in any of the above rejections. Therefore, Applicant respectfully submits that the pending claims are allowable, and urges the Examiner to withdraw the rejections.

CONCLUSION

In light of the above, Applicant respectfully submits that pending claims 27, 29-50 and 52 are in condition for allowance. Therefore, Applicant requests that the present rejections be withdrawn, and that the claims be allowed and passed to issue. If any impediment to the allowance of these claims remains after entry of this Amendment, the Examiner is encouraged to call Gary P. Oakeson at (801) 566-6633 so that such matters may be resolved as expeditiously as possible.

The Commissioner is hereby authorized to charge any additional fee or to credit any overpayment in connection with this Amendment to Deposit Account No. 20-0100.

DATED this 8th day of February, 2008.

Respectfully submitted,



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